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L1      28 (ATHEROSCLEROSIS OR ARTERIOSCLEROSIS) (10A) PAPP
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L2      17 DUPLICATE REMOVE L1 (11 DUPLICATES REMOVED)
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    35 FILES SEARCHED...
    57 FILES SEARCHED...
    85 FILES SEARCHED...
L3      17 L2 NOT (COMPLETE GENOME)
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    43 FILES SEARCHED...
    91 FILES SEARCHED...
L4      28 (ATHEROSCLEROSIS OR ARTERIOSCLEROSIS) (10A) PAPP
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    14 FILES SEARCHED...
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=> d l6 1-17 bib ab

L6 ANSWER 1 OF 17 BIOTECHABS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN  
AN 2003-21068 BIOTECHABS

TI New transgenic mice having a disruption of an endogenous PAPP-A gene,  
useful as an animal model for studying the biological role of  
**PAPP-A** genes in e.g. wound healing, bone remodeling, cancer,  
**atherosclerosis** or fetal development;  
vector-mediated gene transfer and expression in embryonic stem cell  
for transgenic mouse construction for use as an animal model for  
disease therapy

AU CONOVER C A; VAN DEURSEN J M A

PA MAYO FOUND MEDICAL EDUCATION and RES

PI WO 2003057864 17 Jul 2003

AI WO 2003-US115 3 Jan 2003

PRAI US 2002-345709 4 Jan 2002; US 2002-345709 4 Jan 2002

DT Patent

LA English

OS WPI: 2003-577523 [54]

AB DERWENT ABSTRACT:

NOVELTY - A transgenic rodent whose genome comprises a disruption of an  
endogenous PAPP-A gene resulting in reduced weight relative to a  
corresponding control rodent, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1)  
progeny of the transgenic rodent; (2) cells isolated from the transgenic  
rodent; (3) a nucleic acid vector comprising a PAPP-A polynucleotide  
disrupted by a marker polynucleotide; and (4) a nucleic acid vector  
comprising a PAPP-A polynucleotide lacking exon 4.

BIOTECHNOLOGY - Preferred Rodent: The rodent is preferably a mouse.  
The disruption in the PAPP-A gene is heterozygous or homozygous, and  
affects an exon within the endogenous PAPP-A gene, where the exon is exon  
4. The corresponding control rodent is a wild type control rodent, and  
has a genome comprising a heterozygous disruption in the endogenous  
PAPP-A gene. The transgenic rodent is deficient in apolipoprotein E.

USE - The transgenic rodent is useful as an animal model for  
studying the biological role of **PAPP-A** gene in wound healing,  
bone remodeling, cancer, **atherosclerosis**, fetal development,  
longevity, follicular development, vascular restenosis, low birth  
weights, and fracture repair. These animals may also be used to screen,  
e.g. toxicity of compounds that are PAPP-A substrates, drugs that alter  
PAPP-A activity, or compounds that alter both pregnancy and non-pregnancy  
conditions related to PAPP-A activity.

EXAMPLE - A knockout construct was made using a portion of mouse  
genomic DNA encoding PAPP-A, which included exon 4 of the PAPP-A gene. A  
neomycin-resistant gene cassette was used to replace 1.6 kb of PAPP-A  
gene sequence including most of exon 4, resulting in the neo cassette  
being flanked by a 6-kb PstI (P) fragment and a 2-kb NsiI (N) fragment of  
mouse PAPP-A locus DNA. Linearized replacement vector DNA was introduced  
into 129-derived mouse embryonic stem cells seeded and selected on feeder  
layers of irradiated fibroblasts in the presence of 350 micrograms/ml  
G418 and 0.2 microM FIAU. After 9 days, 100-500 clones were picked and  
expanded. DNA extracted from the cells was digested with BamHI, run on  
agarose gel, and transferred to Hybond membranes pre-hybridized for 1  
hour, and hybridized overnight in the same solution containing  
32P-labeled 3' probe. DNA from control exhibited a single 15 kb band,  
heterozygous cells exhibited both 15 kb and 2.6 kb bands, and homozygous  
mutant cells exhibited a single 2.6 kb band. After genotyping, 4  
independent homozygous mutant clones were expanded, harvested, and then  
microinjected into blastocysts of C57BL/6 mice. Injected blastocysts were  
transferred into the uterine horn of surrogate mothers to generate  
chimera mice. Male chimeras from 3 of the 4 clones were then cross-bred

with C57BL/6 females and germ-line transmission was obtained for all 3. Identified heterozygous mice were bred and crossed to produce progenies, which were genotyped using tail tip DNA and Southern analysis technique. Of the 170 F1 progenies analyzed, 34 were wild type, 89 were heterozygous, and 43 were homozygous for the disrupted allele. Homozygous PAPP-A-deficient mice were smaller than their wild type littermates. (12 pages)

L6 ANSWER 2 OF 17 USPATFULL on STN DUPLICATE 2  
AN 2003:3486 USPATFULL  
TI Marker for inflammatory conditions  
IN Holmes, David R., Rochester, MN, UNITED STATES  
Schwartz, Robert S., Rochester, MN, UNITED STATES  
PA Mayo Foundation for Medical Education and Research a Minnesota corporation (U.S. corporation)  
PI US 2003003521 A1 20030102  
US 6699675 B2 20040302  
AI US 2002-210339 A1 20020731 (10)  
RLI Division of Ser. No. US 2001-760376, filed on 12 Jan 2001, PENDING  
DT Utility  
FS APPLICATION  
LREP MARK S. ELLINGER, PH.D., Fish & Richardson P.C.. P.A., Suite 3300, 60 South Sixth Street, Minneapolis, MN, 55402  
CLMN Number of Claims: 22  
ECL Exemplary Claim: 1  
DRWN 5 Drawing Page(s)  
LN.CNT 902  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB Use of pregnancy-associated plasma protein-A as a marker for inflammatory conditions, and in particular, for acute coronary syndromes is described.

L6 ANSWER 3 OF 17 USPATFULL on STN  
AN 2003:180700 USPATFULL  
TI Pregnancy-associated plasma protein-A2 (PAPP-A2)  
IN Oxvig, Claus, Viby, DENMARK  
Overgaard, Michael Toft, Aarhus C., DENMARK  
PA Como Biotech ApS, Aarhus C., DENMARK (non-U.S. corporation)  
PI US 2003124529 A1 20030703  
AI US 2001-983025 A1 20011022 (9)  
PRAI DK 2000-1571 20001020  
US 2000-241840P 20001020 (60)  
DT Utility  
FS APPLICATION  
LREP BROWDY AND NEIMARK, P.L.L.C., 624 Ninth Street, N.W., Washington, DC, 20001  
CLMN Number of Claims: 67  
ECL Exemplary Claim: 1  
DRWN 11 Drawing Page(s)  
LN.CNT 3811  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB The present invention provides nucleotide and amino acid sequences that identify and encode a new protein with homology to pregnancy-associated plasma protein-A (PAPP-A). We denote this protein PAPP-A2. The cDNA encoding PAPP-A2 was derived from human placenta. The present invention also provides for antisense molecules to the nucleotide sequences which encode PAPP-A2, expression vectors for the production of purified PAPP-A2, antibodies capable of binding specifically to PAPP-A2, hybridization probes or oligonucleotides for the detection of PAPP-A2-encoding nucleotide sequences, genetically engineered host cells for the expression of PAPP-A2, use of the protein to produce antibodies capable of binding specifically to the protein, methods for screening for pathologies in pregnant and non-pregnant patients that are based on detection of PAPP-A2 antigen in human body fluids or PAPP-A2-encoding

nucleic acid molecules, use of the protein to screen for agents that alter the protease activity of PAPP-A2, use of the protein as a therapeutic target for such agents, and use of the protein as a therapeutic agent in relevant pathological states. Methods for screening for altered focal proliferation states in pregnant and/or non-pregnant patients, which include detecting levels of PAPP-A2, are also described. The present invention also provides the identification of a natural substrate of PAPP-A2, insulin-like growth factor binding protein (IGFBP)-5.

L6 ANSWER 4 OF 17 EMBAL COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on  
STN DUPLICATE 3

AN 2004043288 EMBASE Alert (EMBAL)

TI [Carotid System - A "Window" in an Atherosclerotic Process in Diabetics?].  
KAROTICKE POVODI - "OKNO" ATEROSKLEROTIEKE HO PROCESU U DIABETIKU?.

AU Adamikova A.

CS Dr. A. Adamikova, Diabetologicke Centrum, Batovy Krajske Nemocnice,  
Havlickovo nabrezi 600, 762 75 Zlin, Czech Republic

SO Vnitřní Lekarství, (2003) 49/12 (967-971). Refs: 20.

CODEN: VNLEA ISSN: 0042-773X

CY Czech Republic

DT Article

LA Czech

SL English; Czech

AB Macrovascular complications present from the viewpoint of morbidity and mortality the biggest risk in type 2 diabetics. An aim of this work is to show ways of detecting clinical and preclinical phases of atherosclerosis with special regard to carotid system. In our paper we have been presenting a sample of 239 patients with cardiovascular incidents and findings on their extracranial carotid systems detected by duplex sonography. 88 patients (36.8 %) in the sample had type 2 diabetes, their average age was  $68.2 \pm 8.5$ . 35 were on a diet, 34 were treated with peroral antidiabetics, and 19 with insulin. Findings on extracranial carotid systems were normal in 27.3 % of diabetics, in stenoses up to 50 % was lumen in 50 %, in stenoses 51-70 % was lumen in 15.9 %, and in stenoses 71-95 % was lumen in 6.8 % (compared to 3.9 in nondiabetics). Intimomedial thickness (IMT) in a group with positive microalbuminuria was  $0.9 \pm 0.3$  mm and in a group with negative microalbuminuria  $0.87 \pm 0.18$  mm. Intimomedial thickness (IMT) and microalbuminuria (MAU) are the markers of risk for atherosclerosis and enable to detect preclinical stages of atherosclerosis. Another enzyme indicated in the process of atherosclerosis is PAPP-A, an indicator of plaque instability. Early detection and early intervention of the atherosclerotic process can prevent growth of atherosclerosis, especially during epidemic increase of type 2 diabetes.

L6 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:935015 CAPLUS

DN 139:78802

TI PAPP-A, a novel marker of unstable plaque, is not influenced by  
hypolipidemic treatment in contrast to CRP

AU Ceska, Richard; Stulc, Tomas; Zima, Tomas; Malbohan, Ivan; Fialova, Lenka  
CS First Faculty of Medicine, Third Department of Internal Medicine, Charles  
University, Prague, 128-21, Czech Rep.

SO Atherosclerosis (Shannon, Ireland) (2003), 166(1), 195-196

CODEN: ATHSBL; ISSN: 0021-9150

PB Elsevier Science Ireland Ltd.

DT Journal

LA English

AB The serum levels of pregnancy-associated plasma protein A and the inflammatory mediator CRP were measured in patients with hyperlipidemia before and after various lipid lowering therapies. Circulating PAPP-A levels were not influenced by lipid lowering in these patients. PAPP-A levels were normal in these patients even in the presence of severe

stabilized atherosclerosis. Unlike PAPP-A, CRP decreased significantly after hypolipidemic treatments. The results indicate that PAPP-A is probably not a suitable marker of increased risk in patients without unstable plaques.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 17 ADISCTI COPYRIGHT (C) 2004 Adis Data Information BV on STN  
DUPLICATE 4

AN 2004:401 ADISCTI

DN 800954352

TI Increased levels of pregnancy-associated plasma protein-A in patients with  
hypercholesterolemia: the effect of atorvastatin treatment.

ADIS TITLE: Atorvastatin: pharmacodynamics.

Effects on pregnancy-associated plasma protein-A levels

In patients with hypercholesterolaemia.

AU Stulc T; Malbohan I; Malik J; Fialova L; Soukupova J; et al.

CS Charles University, Prague, Czech Republic.

SO American Heart Journal Electronic Pages [serial online] (Dec 1, 2003),  
Vol. 146, No. 6, pp. e21

DT Study

RE Hyperlipidaemia

FS Summary

LA English

WC 589

L6 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5

AN 2003:187 CAPLUS

DN 138:235929

TI Serum Plasma Pregnancy-Associated Protein A

AU Beaudeau, Jean-Louis; Burc, Laurence; Imbert-Bismut, Francoise; Giral,  
Philippe; Bernard, Maguy; Bruckert, Eric; Chapman, M. John

CS Department of Clinical Biochemistry, The National Institute for Health and  
Medical Research INSERM U551, Paris, Fr.

SO Arteriosclerosis, Thrombosis, and Vascular Biology (2003), 23(1), e7-e10  
CODEN: ATVBFA; ISSN: 1079-5642

PB Lippincott Williams & Wilkins

DT Journal

LA English

AB The proteolytic activity of metalloproteinases, proinflammatory enzymes  
that degrade extracellular matrix, is elevated in lipid-rich  
atherosclerotic plaques, thereby contributing to plaque fragility and  
rupture. Pregnancy-associated plasma protein (PAPP-A) is a  
metalloproteinase, expressed in unstable atherosclerotic plaques, whose  
circulating levels are elevated in acute coronary syndromes. We evaluated  
serum PAPP-A levels as a marker of the premature development of  
**atherosclerosis** in hyperlipidemic subjects at elevated  
cardiovascular risk.

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 17 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED.  
on STN

AN 2003-0132200 PASCAL

CP Copyright .COPYRGT. 2003 INIST-CNRS. All rights reserved.

TIEN Serum plasma pregnancy-associated protein A: A potential marker of  
echogenic carotid atherosclerotic plaques in asymptomatic hyperlipidemic  
subjects at high cardiovascular risk

AU BEAUDEUX Jean-Louis; BURC Laurence; IMBERT-BISMUT Francoise; GIRAL  
Philippe; BERNARD Maguy; BRUCKERT Eric; CHAPMAN M. John

SO Arteriosclerosis, thrombosis, and vascular biology, (2003), 23(1), p. 76  
ISSN: 1079-5642 CODEN: ATVBFA

DT Journal; (summary); Short communication

BL Analytic

CY United States  
LA English  
AV INIST-19104, 354000103804350140  
AB Objective-The proteolytic activity of metalloproteinases, proinflammatory enzymes that degrade extracellular matrix, is elevated in lipid-rich atherosclerotic plaques, thereby contributing to plaque fragility and rupture. Pregnancy-associated plasma protein (PAPP-A) is a metalloproteinase, expressed in unstable atherosclerotic plaques, whose circulating levels are elevated in acute coronary syndromes. We evaluated serum PAPP-A levels as a marker of the premature development of **atherosclerosis** in hyperlipidemic subjects at elevated cardiovascular risk. Methods and Results-Serum PAPP-A levels were determined in asymptomatic hyperlipidemic male subjects (n=64; mean±SD age, 51±7 years) in whom intima-media thickness (IMT) and lesion status in the carotid artery were evaluated by noninvasive ultrasonography and compared with those of a normolipidemic control group (n=25). No difference was observed in circulating PAPP-A levels between hyperlipidemic subjects and controls (8.99±2.93 and 8.03±2.75 mIU/L, respectively; mean±SD) nor between hyperlipidemic subjects who presented with a luminal obstruction of the carotid artery (9.26±2.53 mIU/L) and those who did not (8.85±3.29 mIU/L). By contrast, in patients with atheromatous carotid plaques, a positive association between serum levels of PAPP-A and C-reactive protein was observed (P<0.05); moreover, subjects exhibiting hyperechoic or isoechoic, echogenic lesions had significantly higher PAPP-A levels compared with those with hypoechoic lesions (10.32±2.72 vs 8.27±2.18 mIU/L, P<0.05) and with normolipidemic controls (P<0.05). Conclusions-Elevated serum PAPP-A levels represent a potential marker of the degree of echogenicity of carotid atherosclerotic plaques in asymptomatic hyperlipidemic patients at high cardiovascular risk and equally of an enhanced local inflammatory state involving remodeling of subendothelial extracellular matrix.

L6 ANSWER 9 OF 17 USPATFULL on STM DUPLICATE 6  
AN 2002:243092 USPATFULL  
TI MARKER FOR INFLAMMATORY CONDITIONS  
IN Conover, Cheryl A., Rochester, MN, UNITED STATES  
Bayes-Genis, Antonio, Barcelona, SPAIN  
Holmes, David R., Rochester, MN, UNITED STATES  
Schwartz, Robert S., Rochester, MN, UNITED STATES  
PI US 2002132278 A1 20020919  
US 6500630 B2 20021231  
AI US 2001-760376 A1 20010112 (9)  
DT Utility  
FS APPLICATION  
LREP MARK S. ELLINGER, Fish & Richardson P.C., P.A., 60 South Sixth Street,  
Suite 3300, Minneapolis, MN, 55402  
CLMN Number of Claims: 22  
ECL Exemplary Claim: 1  
DRWN 5 Drawing Page(s)  
LN.CNT 901  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB Use of pregnancy-associated plasma protein-A as a marker for  
inflammatory conditions, and in particular, for acute coronary syndromes  
is described.  
L6 ANSWER 10 OF 17 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STM DUPLICATE 7  
AN 2002305837 EMBASE  
TI Pregnancy-associated plasma protein A as a marker of acute coronary  
syndromes.  
AU Bayes-Genis A.; Conover C.A.; Overgaard M.T.; Bailey K.R.; Christiansen  
M.; Holmes Jr. D.R.; Virmani R.; Oxvig C.; Schwartz R.S.  
CS Dr. R.S. Schwartz, Division of Cardiovascular Diseases, Mayo Clinic, 200

First St., SW, Rochester, MN 55905, United States  
SO New England Journal of Medicine, (4 Oct 2001) 345/14 (1022-1029).  
Refs: 32  
ISSN: 0028-4793 CODEN: NEJMAG

CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy

018 Cardiovascular Diseases and Cardiovascular Surgery

LA English

SL English

AB Background: Circulating markers indicating the instability of atherosclerotic plaques could have diagnostic value in unstable angina or acute myocardial infarction. We evaluated pregnancy-associated plasma protein A (PAPP-A), a potentially proatherosclerotic metalloproteinase, as a marker of acute coronary syndromes. Methods: We examined the level of expression of PAPP-A in eight culprit unstable coronary plaques and four stable plaques from eight patients who had died suddenly of cardiac causes. We also measured circulating levels of PAPP-A, C-reactive protein, and insulin-like growth factor I (IGF-I) in 17 patients with acute myocardial infarction, 20 with unstable angina, 19 with stable angina, and 13 controls without atherosclerosis. Results: PAPP-A was abundantly expressed in plaque cells and extracellular matrix of ruptured and eroded unstable plaques, but not in stable plaques. Circulating PAPP-A levels were significantly higher in patients with unstable angina or acute myocardial infarction than in patients with stable angina and controls ( $P < 0.001$ ). A PAPP-A threshold value of 10 mIU per liter identified patients who had acute coronary syndromes with a sensitivity of 89.2 percent and a specificity of 81.3 percent. PAPP-A levels correlated with levels of C-reactive protein and free IGF-I, but not with markers of myocardial injury (troponin I and the MB isoform of creatine kinase). Conclusions: PAPP-A is present in unstable plaques, and circulating levels are elevated in acute coronary syndromes; these increased levels may reflect the instability of atherosclerotic plaques. PAPP-A is a new candidate marker of unstable angina and acute myocardial infarction. Copyright .COPYRG. 2001 Massachusetts Medical Society.

L6 ANSWER 11 OF 17 ADISNEWS COPYRIGHT (C) 2004 Adis Data Information BV on STN

AN 2001:4593 ADISNEWS ED 11 Oct 2001 UP 11 Oct 2001

DN 11738324-800840893

TI Product news: Promising new markers for acute coronary syndromes.

SO INPHARMA 11 Oct 2001 ISSN: 1173-8324

DT (MIX)

WC 390

L6 ANSWER 12 OF 17 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN

AN AAB23246 peptide DGENE

TI Screening or diagnosing a growth promoting state e.g. restenosis, atherosclerosis, wound healing, osteoporosis and cancer in a non-pregnant patient, comprises detecting levels of pregnancy-associated plasma protein-A -

IN Overgaard M T; Oxvig C; Conover C A

PA (MAYO-N) MAYO FOUND MEDICAL EDUCATION & RES.

(OVER-I) OVERGAARD M T.

(OXVI-I) OXVIG C.

PI WO 2000054806 A1 20000921 55p

AI WO 2000-US6728 20000315

PRAI US 1999-124541 19990315

DT Patent

LA English

OS 2000-647055 [62]

DESC Human PAPP-A (IGFBP-4 protease) peptide, SEQ ID NO:6.

AB The invention relates to a method of screening or diagnosing a altered growth state (focal proliferation state) in a non-pregnant patient. The

method comprises detecting the level of pregnancy-associated plasma protein-A (PAPP-A) in a biological sample and comparing the level of PAPP-A to the level of PAPP-A in healthy non-pregnant patients. An increase in the level of PAPP-A indicates the presence of a growth-promoting state, while a decrease in the level of PAPP-A indicates the presence of a growth-inhibiting state. The invention also relates to a monoclonal antibody (Mab) specific to PAPP-A, wherein PAPP-A is free from pro-major basic protein (proMBP) and methods of identifying modulators of PAPP-A activity. The invention discloses the identification of PAPP-A as an insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease (IGFBP-4 protease). IGFBP-4 is a potent inhibitor of IGF stimulatory effects, which suggests PAPP-A activity acts as a positive regulator of IGF bioavailability. The method of the invention may be used to screen or diagnose a growth promoting state such as restenosis, atherosclerosis, ovulation, wound healing, fibrosis or cancer, or a growth inhibiting state such as osteoporosis, in a non-pregnant patient. Inhibitors of PAPP-A proteolytic activity are useful for treating disorders such as restenosis, **atherosclerosis** and fibrosis. Sequences AAB23241-B23246 represent **PAPP-A** (IGFBP-4 protease) peptides used in an exemplification of the invention.

L6 ANSWER 13 OF 17 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN  
AN AAB23245 peptide DGENE  
TI Screening or diagnosing a growth promoting state e.g. restenosis, atherosclerosis, wound healing, osteoporosis and cancer in a non-pregnant patient, comprises detecting levels of pregnancy-associated plasma protein-A -  
IN Overgaard M T; Oxvig C; Conover C A  
PA (MAYO-N) MAYO FOUND MEDICAL EDUCATION & RES.  
(OVER-I) OVERGAARD M T.  
(OXVI-I) OXVIG C.  
PI WO 2000054806 A1 20000921 55p  
AI WO 2000-US6728 20000315  
PRAI US 1999-124541 19990315  
DT Patent  
LA English  
OS 2000-647055 [62]  
DESC Human PAPP-A (IGFBP-4 protease) peptide, SEQ ID NO:5.  
AB The invention relates to a method of screening or diagnosing a altered growth state (focal proliferation state) in a non-pregnant patient. The method comprises detecting the level of pregnancy-associated plasma protein-A (PAPP-A) in a biological sample and comparing the level of PAPP-A to the level of PAPP-A in healthy non-pregnant patients. An increase in the level of PAPP-A indicates the presence of a growth-promoting state, while a decrease in the level of PAPP-A indicates the presence of a growth-inhibiting state. The invention also relates to a monoclonal antibody (Mab) specific to PAPP-A, wherein PAPP-A is free from pro-major basic protein (proMBP) and methods of identifying modulators of PAPP-A activity. The invention discloses the identification of PAPP-A as an insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease (IGFBP-4 protease). IGFBP-4 is a potent inhibitor of IGF stimulatory effects, which suggests PAPP-A activity acts as a positive regulator of IGF bioavailability. The method of the invention may be used to screen or diagnose a growth promoting state such as restenosis, atherosclerosis, ovulation, wound healing, fibrosis or cancer, or a growth inhibiting state such as osteoporosis, in a non-pregnant patient. Inhibitors of PAPP-A proteolytic activity are useful for treating disorders such as restenosis, **atherosclerosis** and fibrosis. Sequences AAB23241-B23246 represent **PAPP-A** (IGFBP-4 protease) peptides used in an exemplification of the invention.

L6 ANSWER 14 OF 17 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN  
AN AAB23244 peptide DGENE  
TI Screening or diagnosing a growth promoting state e.g. restenosis,

atherosclerosis, wound healing, osteoporosis and cancer in a non-pregnant patient, comprises detecting levels of pregnancy-associated plasma protein-A -

IN Overgaard M T; Oxvig C; Conover C A  
PA (MAYO-N) MAYO FOUND MEDICAL EDUCATION & RES.  
(OVER-I) OVERGAARD M T.  
(OXVI-I) OXVIG C.

PI WO 2000054806 A1 20000921 55p

AI WO 2000-US6728 20000315

PRAI US 1999-124541 19990315

DT Patent

LA English

OS 2000-647055 [62]

DESC Human PAPP-A (IGFBP-4 protease) peptide, SEQ ID NO:4.

AB The invention relates to a method of screening or diagnosing a altered growth state (focal proliferation state) in a non-pregnant patient. The method comprises detecting the level of pregnancy-associated plasma protein-A (PAPP-A) in a biological sample and comparing the level of PAPP-A to the level of PAPP-A in healthy non-pregnant patients. An increase in the level of PAPP-A indicates the presence of a growth-promoting state, while a decrease in the level of PAPP-A indicates the presence of a growth-inhibiting state. The invention also relates to a monoclonal antibody (Mab) specific to PAPP-A, wherein PAPP-A is free from pro-major basic protein (proMBP) and methods of identifying modulators of PAPP-A activity. The invention discloses the identification of PAPP-A as an insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease (IGFBP-4 protease). IGFBP-4 is a potent inhibitor of IGF stimulatory effects, which suggests PAPP-A activity acts as a positive regulator of IGF bioavailability. The method of the invention may be used to screen or diagnose a growth promoting state such as restenosis, atherosclerosis, ovulation, wound healing, fibrosis or cancer, or a growth inhibiting state such as osteoporosis, in a non- pregnant patient. Inhibitors of PAPP-A proteolytic activity are useful for treating disorders such as restenosis, **atherosclerosis** and fibrosis. Sequences AAB23241-B23246 represent **PAPP-A** (IGFBP-4 protease) peptides used in an exemplification of the invention.

L6 ANSWER 15 OF 17 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN

AN AAB23243 peptide DGENE

TI Screening or diagnosing a growth promoting state e.g. restenosis, atherosclerosis, wound healing, osteoporosis and cancer in a non-pregnant patient, comprises detecting levels of pregnancy-associated plasma protein-A -

IN Overgaard M T; Oxvig C; Conover C A  
PA (MAYO-N) MAYO FOUND MEDICAL EDUCATION & RES.  
(OVER-I) OVERGAARD M T.  
(OXVI-I) OXVIG C.

PI WO 2000054806 A1 20000921 55p

AI WO 2000-US6728 20000315

PRAI US 1999-124541 19990315

DT Patent

LA English

OS 2000-647055 [62]

DESC Human PAPP-A (IGFBP-4 protease) peptide, SEQ ID NO:3.

AB The invention relates to a method of screening or diagnosing a altered growth state (focal proliferation state) in a non-pregnant patient. The method comprises detecting the level of pregnancy-associated plasma protein-A (PAPP-A) in a biological sample and comparing the level of PAPP-A to the level of PAPP-A in healthy non-pregnant patients. An increase in the level of PAPP-A indicates the presence of a growth-promoting state, while a decrease in the level of PAPP-A indicates the presence of a growth-inhibiting state. The invention also relates to a monoclonal antibody (Mab) specific to PAPP-A, wherein PAPP-A is free from pro-major basic protein (proMBP) and methods of identifying modulators of



PAPP-A activity. The invention discloses the identification of PAPP-A as an insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease (IGFBP-4 protease). IGFBP-4 is a potent inhibitor of IGF stimulatory effects, which suggests PAPP-A activity acts as a positive regulator of IGF bioavailability. The method of the invention may be used to screen or diagnose a growth promoting state such as restenosis, atherosclerosis, ovulation, wound healing, fibrosis or cancer, or a growth inhibiting state such as osteoporosis, in a non-pregnant patient. Inhibitors of PAPP-A proteolytic activity are useful for treating disorders such as restenosis, **atherosclerosis** and fibrosis. Sequences AAB23241-B23246 represent **PAPP-A** (IGFBP-4 protease) peptides used in an exemplification of the invention.

L6 ANSWER 16 OF 17 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN  
 AN AAB23242 peptide DGENE  
 TI Screening or diagnosing a growth promoting state e.g. restenosis, atherosclerosis, wound healing, osteoporosis and cancer in a non-pregnant patient, comprises detecting levels of pregnancy-associated plasma protein-A -  
 IN Overgaard M T; Oxvig C; Conover C A  
 PA (MAYO-N) MAYO FOUND MEDICAL EDUCATION & RES.  
 (OVER-I) OVERGAARD M T.  
 (OXVI-I) OXVIG C.  
 PI WO 2000054806 A1 20000921 55p  
 AI WO 2000-US6728 20000315  
 PRAI US 1999-124541 19990315  
 DT Patent  
 LA English  
 OS 2000-647055 [62]  
 DESC Human PAPP-A (IGFBP-4 protease) peptide, SEQ ID NO:2.  
 AB The invention relates to a method of screening or diagnosing a altered growth state (focal proliferation state) in a non-pregnant patient. The method comprises detecting the level of pregnancy-associated plasma protein-A (PAPP-A) in a biological sample and comparing the level of PAPP-A to the level of PAPP-A in healthy non-pregnant patients. An increase in the level of PAPP-A indicates the presence of a growth-promoting state, while a decrease in the level of PAPP-A indicates the presence of a growth-inhibiting state. The invention also relates to a monoclonal antibody (MAb) specific to PAPP-A, wherein PAPP-A is free from pro-major basic protein (proMBP) and methods of identifying modulators of PAPP-A activity. The invention discloses the identification of PAPP-A as an insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease (IGFBP-4 protease). IGFBP-4 is a potent inhibitor of IGF stimulatory effects, which suggests PAPP-A activity acts as a positive regulator of IGF bioavailability. The method of the invention may be used to screen or diagnose a growth promoting state such as restenosis, atherosclerosis, ovulation, wound healing, fibrosis or cancer, or a growth inhibiting state such as osteoporosis, in a non-pregnant patient. Inhibitors of PAPP-A proteolytic activity are useful for treating disorders such as restenosis, **atherosclerosis** and fibrosis. Sequences AAB23241-B23246 represent **PAPP-A** (IGFBP-4 protease) peptides used in an exemplification of the invention.

L6 ANSWER 17 OF 17 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN  
 AN AAB23241 peptide DGENE  
 TI Screening or diagnosing a growth promoting state e.g. restenosis, atherosclerosis, wound healing, osteoporosis and cancer in a non-pregnant patient, comprises detecting levels of pregnancy-associated plasma protein-A -  
 IN Overgaard M T; Oxvig C; Conover C A  
 PA (MAYO-N) MAYO FOUND MEDICAL EDUCATION & RES.  
 (OVER-I) OVERGAARD M T.  
 (OXVI-I) OXVIG C.  
 PI WO 2000054806 A1 20000921 55p

AI WO 2000-US6728 20000315  
PRAI US 1999-124541 19990315  
DT Patent  
LA English  
OS 2000-647055 [62]

DESC Human PAPP-A (IGFBP-4 protease) peptide, SEQ ID NO:1.

AB The invention relates to a method of screening or diagnosing a altered growth state (focal proliferation state) in a non-pregnant patient. The method comprises detecting the level of pregnancy-associated plasma protein-A (PAPP-A) in a biological sample and comparing the level of PAPP-A to the level of PAPP-A in healthy non-pregnant patients. An increase in the level of PAPP-A indicates the presence of a growth-promoting state, while a decrease in the level of PAPP-A indicates the presence of a growth-inhibiting state. The invention also relates to a monoclonal antibody (MAb) specific to PAPP-A, wherein PAPP-A is free from pro-major basic protein (proMBP) and methods of identifying modulators of PAPP-A activity. The invention discloses the identification of PAPP-A as an insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease (IGFBP-4 protease). IGFBP-4 is a potent inhibitor of IGF stimulatory effects, which suggests PAPP-A activity acts as a positive regulator of IGF bioavailability. The method of the invention may be used to screen or diagnose a growth promoting state such as restenosis, atherosclerosis, ovulation, wound healing, fibrosis or cancer, or a growth inhibiting state such as osteoporosis, in a non- pregnant patient. Inhibitors of PAPP-A proteolytic activity are useful for treating disorders such as restenosis, **atherosclerosis** and fibrosis. Sequences AAB23241-B23246 represent **PAPP-A** (IGFBP-4 protease) peptides used in an exemplification of the invention.